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New Methods

Detection of Subclinical Coronary Atherosclerosis Using Two-Dimensional, High-Resolution Transthoracic Echocardiography

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OBJECTIVES We evaluated whether two-dimensional high-resolution transthoracic echocardiography (HR-2DTTE) can detect changes in arterial wall thickness and size associated with subclinical coronary artery disease (CAD).

BACKGROUND Arterial wall thickening, compensatory arterial enlargement and a preserved arterial lumen characterize subclinical atherosclerosis. Detection of these changes during the asymptomatic stage of CAD may allow early treatment and prevention of acute coronary events.

METHODS Twenty-six patients with angiographically proven CAD and 29 normal volunteers underwent HR-2DTTE evaluation of the left anterior descending coronary artery (LAD) using an ATL 5000 echograph (Advanced Technology Laboratories, Bothell, Washington) with a 4 to 7 MHz transducer. Significant (>70%) LAD stenosis was present in 15 patients (mean 82%); 11 patients did not have significant LAD stenosis (mean 26%) and represented a surrogate for subclinical LAD disease. Wall thickness, maximal luminal diameter and external diameter of the LAD were measured.

RESULTS Left anterior descending coronary artery wall thickness was larger in patients (1.9 ± 0.4 mm) than it was in volunteers (0.9 ± 0.1 mm, $p < 0.001$). The external diameter of the LAD was (6.0 ± 1.1 mm) in patients and (3.9 ± 0.7 mm) in volunteers ($p < 0.001$). Luminal diameter was 2.2 ± 0.5 mm in patients and 2.1 ± 0.6 mm in volunteers (p = NS). There was no difference in wall thickness (1.9 ± 0.4 mm vs. 2.0 ± 0.4 mm), luminal diameter (2.2 ± 0.5 mm vs. 2.2 ± 0.4 mm) and external diameter (5.9 ± 1.0 mm vs. 6.2 ± 1.2 mm) between the patients with <70% and >70% LAD stenosis.

CONCLUSIONS Left anterior descending coronary artery wall thickness and external diameter are significantly increased in patients with CAD as compared with normal subjects, and HR-2DTTE is sensitive enough to detect these differences. Wall thickness and external diameter are increased to the same extent in patients with obstructive and subclinical LAD disease. (J Am Coll Cardiol 2001;37:1422–9) © 2001 by the American College of Cardiology

Atherosclerosis is a slowly progressive disease affecting the walls of the coronary arteries as well as other large and medium size muscular arteries. Early in the course of atherosclerosis, progressive thickening of the arterial wall is compensated for by outward arterial remodeling, resulting in arterial enlargement and preservation of the arterial lumen (1–5). Some studies suggest that it is only in the advanced stage of the disease, when plaque occupies more than 30% to 40% of the vessel area, that this compensatory mechanism fails, and there is progressive luminal narrowing (1,6). These findings suggest that changes in the size of the coronary artery lumen are not adequate for the diagnosis of subclinical coronary atherosclerosis because the disease is present in the arterial wall before luminal changes are evident. In addition, evaluation of atherosclerosis based solely on assessment of lumen size has limited prognostic value since coronary atherosclerotic plaques vulnerable to rupture often are not associated with high-grade luminal stenosis (7,8), and there is an inconsistent relationship between the severity of the coronary artery stenosis and the future infarct site (9). Failure to detect the early changes of atherosclerosis results in a missed opportunity for intervention. Detection of subclinical, nonobstructive coronary artery disease (CAD) will require the evaluation of coronary arterial walls and external coronary diameter in order to detect increases in arterial wall thickness and compensatory remodeling. The optimal method for detection of subclinical disease should be noninvasive and relatively inexpensive.

The proximal coronary arteries, specifically the left main coronary artery and its proximal branches, have been identified with two-dimensional transthoracic echocardiography (2DTTE) using short-axis views for two decades (10–14). Successful application of this technique to the detection of left main and left anterior descending coronary artery (LAD) atherosclerosis has been described (11–16). Recent advances in imaging technique and technology have increased the potential for successful visualization of the coronary arteries. It was recently demonstrated that stents in the LAD can be imaged along the septum in the parasternal

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Abbreviations and Acronyms

ANCOVA	=	analysis of covariance
CAD	=	coronary artery disease
HR-2DTTE	=	high resolution, two-dimensional transthoracic echocardiography
IVUS	=	intravascular ultrasound
LAD	=	left anterior descending coronary artery
MRI	=	magnetic resonance imaging
2DTTE	=	two-dimensional transthoracic echocardiography

long-axis view using three-dimensionally acquired, two-dimensionally displayed transthoracic echocardiography (17). We applied this imaging technique to 2DTTE and realized that, in the parasternal long-axis view, relatively long segments of the vessel can be seen and measured. Image quality also has improved due to new broadband, high-resolution transducers, making measurements more reliable.

Since CAD is a diffuse process and it rarely spares the proximal LAD (6), this coronary artery segment should represent a good sampling site for the detection of both obstructive and nonobstructive, that is, subclinical, CAD. We postulated that with the use of high-resolution broadband transducers, high-resolution, two-dimensional transthoracic echocardiography (HR-2DTTE) would have adequate penetration and resolution to evaluate the walls of the coronary arteries and to detect increased wall thickness and external diameter of the vessel, changes that are indicative of subclinical coronary atherosclerosis.

METHODS

The Institutional Review Board of the Indiana University School of Medicine approved the study protocol. All subjects read and signed informed consent.

Study population. Twenty-six randomly selected patients (19 men, age 35 to 82, mean 57 years) who presented for cardiac catheterization in our institution and were found to have significant CAD were asked to participate in the study. The patients' echogenicity was not a factor in their selection. Patients who had coronary artery bypass surgery or percutaneous coronary intervention involving the LAD were excluded from the study. Angiographically significant (>70%) stenosis of the LAD was present in 15 patients with CAD (mean stenosis 82%), while 11 patients had angiographically subclinical disease in the LAD territory (mean stenosis 26%) but significant disease in the other coronary distributions. The 11 patients without significant LAD stenosis were designated as a surrogate for "subclinical" CAD in the LAD distribution. Twenty-nine young volunteers (15 men, age 18 to 33, mean 25 years) who had no risk factors for CAD underwent HR-2DTTE and served as a normal control group.

Echocardiography. Patients underwent transthoracic echocardiography of the coronary arteries within 24 h of cardiac catheterization. The examinations were obtained with a commercially available echograph ATL 5000 and a phased array, broadband transducer with a frequency range of 4 to 7 MHz. The axial resolution provided by a 7 MHz transducer is 0.25 mm at the depth of 5 cm, which is the usual depth of the proximal and mid-LAD from the chest wall surface in humans. The LAD was recorded using a parasternal long-axis examination. The sonographer scanned across the interventricular septum in the long-axis view in order to record as much of the LAD as possible. Echocardiographic recordings of four separate cardiac cycles were captured digitally on-line and displayed in a quad screen format. Each cardiac cycle consisted of 16 frames. The onset of capture was gated to the R wave of the electrocardiogram with subsequent frames captured with 66 ms intervals. The procedure lasted approximately 5 to 10 min. Images were stored in a digital network for off-line retrieval and analysis.

Echocardiographic analysis. Coronary echograms were analyzed off-line by two echocardiographers without knowledge of the subjects' history. The presence of two linear echoes anterior to the interventricular septum in at least three consecutive frames was the criterion used to identify the LAD. When possible, identification of branching vessels was used as an additional criterion. Readers were asked to identify the LAD on the two-dimensional image, perform measurements of the external diameter, luminal size and anterior and posterior LAD wall thickness on the frame where the artery was best seen and where the luminal diameter was the largest. The LAD wall measurements were made from the outer edge to the inner edge of the line representing the vascular wall. The external diameter of the vessel was measured as the distance between the outer edges of the lines representing vascular walls, and luminal diameter was measured as the distance between the inner edges of the lines representing vascular walls. Measurements were made in three separate frames, and the results were averaged. The investigators were free to choose any frames that they felt best visualized the LAD. The decision to measure the segments with the largest lumen was made to ensure that the measured cross-section of the vessel was through the center of the vessel and, thus, the coronary arterial wall thickness was not overestimated by off-axis measurements. We also wanted to obtain the measurement of the largest external diameter of the vessel. The length of the measured segment was also obtained on each measured frame. In addition, readers were asked to count the total number of frames on which the LAD was identified after the first 11 subjects were enrolled into each group.

Coronary angiograms. The cardiologist who performed cardiac catheterization analyzed the coronary angiograms by visually determining the percent diameter stenosis.

Statistical analysis. All results are presented as a mean ± one standard deviation. The differences between the groups were evaluated using the unpaired *t* test. The correlation between the readers was computed, and the significance was

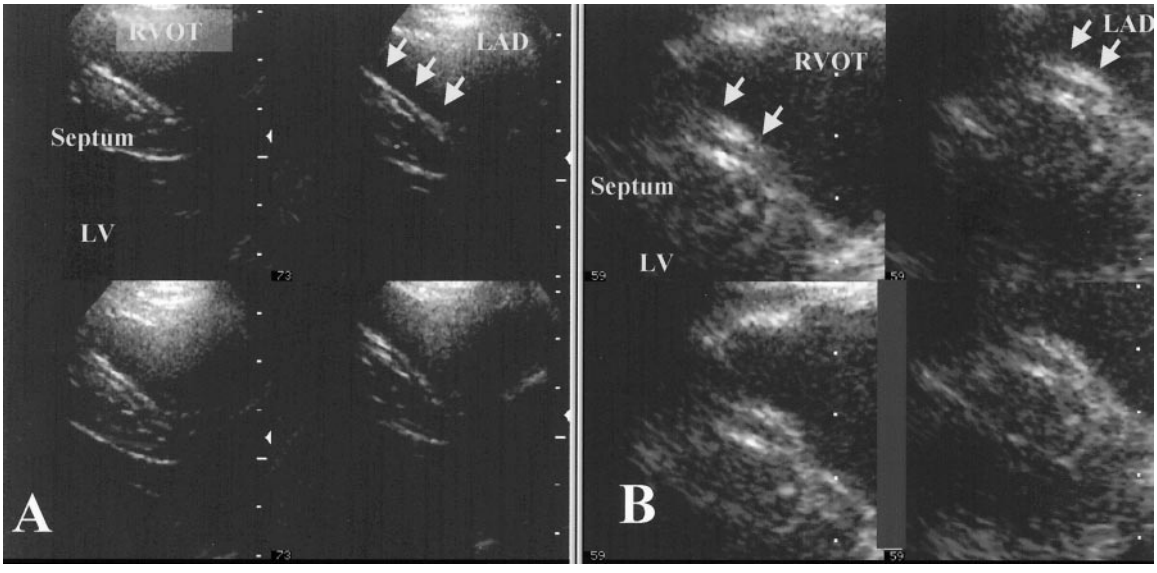

Figure 1. Quad screen presenting the LAD segment from a normal volunteer **(A)** and patient with CAD **(B)**. **Arrows** point to LAD. **Markers** on the side of the frames represent scale in centimeters. CAD = coronary artery disease; LAD = left anterior descending coronary artery; LV = left ventricle; RVOT = right ventricular outflow tract.

tested with a *t* test. The effect of age on wall thickness and external diameter was analyzed using analysis of covariance (ANCOVA).

RESULTS

The two investigators were able to measure the LAD in 54 out of 55 subjects (98%). One patient with significant LAD stenosis had technically inadequate images, and it was not possible to identify the LAD. In most cases, the investigators selected different frames to perform measurements. Figure 1 illustrates an example of the quad view image showing the LAD segment from a normal volunteer (Fig. 1A) and from a patient with CAD (Fig. 1B). The average number of frames on which the LAD was identified was 50 ± 15 (out of maximum 64 frames) in the group of normal volunteers and 42 ± 18 in the group of patients with CAD (p = NS). The average length of the visualized LAD segment in the group with CAD was 15 ± 4 mm and in the group of normal volunteers was 17 ± 3 mm (p = 0.052). The mean LAD wall thickness was 0.9 ± 0.1 mm in the normal volunteer group and 1.9 ± 0.4 mm in patients with CAD. This difference was statistically significant with $p < 0.001$ (Fig. 2A). The mean external diameter of the LAD was 3.9 ± 0.7 mm in normal volunteers and 6.0 ± 1.1 mm in patients with CAD ($p < 0.001$) (Fig. 2A). The mean of the maximal luminal diameter was 2.1 ± 0.6 mm in the group of volunteers and 2.2 ± 0.5 mm in patients with CAD (Fig. 2A). There was no difference in the wall thickness (2.0 ± 0.4 mm vs. 1.9 ± 0.4 mm) maximal luminal diameter (2.2 ± 0.4 mm vs. 2.2 ± 0.5 mm) and external diameter (6.2 ± 1.1 mm vs. 5.9 ± 1.0 mm) between the patients with angiographically subclinical (n = 11) and significant LAD disease (n = 15) as illustrated in Figure 2B. The scatter plot in Figure 3A shows that there was no overlap between the wall thickness in the group of normal volunteers and patients with CAD. In the subjects who participated in our study, the wall thickness of 1.2 mm separated the normal and the diseased group. There is clear diagnostic separation between normal and CAD groups for both readers. Figure 3C shows that there is only small overlap in the external diameter measurements between the group of volunteers and patients, which indicates that the external diameter of the LAD may be used as an additional diagnostic parameter.

Lack of correlation between the two readers in wall thickness measurements for the group of volunteers ($r = 0.20$; p = NS) and weak correlation in the group of patients with CAD ($r = 0.38$; $p < 0.05$) (Fig. 3A) is due to a limited range of variability of wall thickness to 0.5 mm in the group of normal volunteers and 1.5 mm in the group of patients with CAD. It is well known in statistics that restricting the range of variability will reduce the correlation, so the lack of correlation between the readers in this case was due to the very small variability of measured values. When the correlation between the readers was calculated for groups of volunteers and patients together, the correlation was statistically significant ($r = 0.90$; $p < 0.01$), indicating good agreement between the readers, consistent with the correlations on the other two graphs in Figure 3, B and C. There is strong correlation between the two readers in luminal diameter measurements in the normal ($r = 0.75$; $p < 0.001$) and CAD group ($r = 0.82$; $p < 0.001$) (Fig. 3B) and in external diameter measurements in the normal ($r = 0.60$; $p < 0.001$) and CAD groups ($r = 0.70$; $p < 0.001$) (Fig. 3C).

There is also a strong correlation between the wall thickness and size of the external diameter of the vessel in the group of patients with CAD ($r = 0.87$; $p < 0.001$) (Fig.

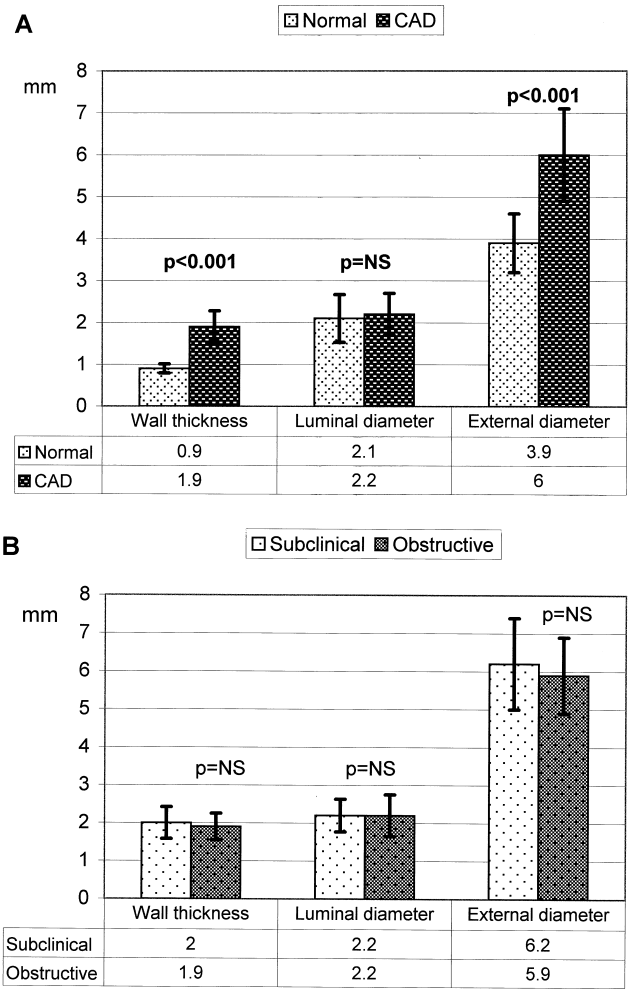

Figure 2. Bar graph illustrating mean measurements of the LAD wall thickness, luminal diameter and external diameter in the groups of normal volunteers and patients with CAD **(A)** and LAD wall thickness, luminal diameter and external diameter in the groups of patients with subclinical and significant (obstructive) LAD disease **(B)**. **Error bars** represent standard deviation. CAD = coronary artery disease; LAD = left anterior descending coronary artery.

4), which confirms that the vessel size increases with increasing wall thickness.

Since our normal control group was not age-matched with the group of patients, wall thickness and external diameter were also plotted against the age of the subjects, to investigate whether the remodeling process is not just related to increasing age. If this were the case, one would expect that the data points from both groups would be adequately approximated by a single regression line with a positive slope. On the other hand, if the age was not a factor in the increasing wall thickness and external diameter, then the measurements from the groups of normal volunteers and patients would be approximated by two parallel horizontal regression lines. To decide between the two possibilities, ANCOVA was applied to wall thickness with age as a concomitant variable. This analysis fitted two regression lines to the data points, one line for the normal group and a second line for patients with CAD. There were three free parameters characterizing the two regression lines: common slope, intercept for normal and intercept for patients with CAD. Figure 5A shows these relations. Regression lines are essentially horizontal with slopes that are not significantly different from zero (p = NS). The same analysis was performed for external diameter, and the results are shown in Figure 5B. Again, the slope of regression lines was not significantly different from zero (p = NS). These results suggest that there is no systematic effect of age on wall thickness and external diameter, which means that age is not a significant factor responsible for the observed differences between normal controls and patients. To test the effect of age directly, an age-matched normal control group of patients should be studied in the future.

DISCUSSION

Early detection of asymptomatic CAD is increasingly important because the initial clinical presentation of CAD is often catastrophic, and effective primary prevention of coronary atherosclerosis is available (18,19). Currently available and recommended methods that are useful in risk stratification of the asymptomatic patient with CAD include the ankle/brachial blood pressure index and B-mode ultrasound of the peripheral arteries. Coronary calcium scores obtained by electron beam computer tomography may be useful in selected patients, and cardiac evaluation with magnetic resonance imaging (MRI), C-reactive protein assay and endothelial function studies are promising new techniques, which will require further development (20).

In our study, evaluation of the LAD walls by HR-2DTTE showed that the LAD walls in patients with documented CAD are significantly thicker than the LAD walls in normal subjects. Also, the external diameter of the LAD was found to be increased in patients with CAD as compared with normal subjects. Our results suggest that HR-2DTTE is sensitive enough to detect those differences. Diseased vascular walls were found not only to be thicker but also more echogenic and irregular in thickness and brightness as compared with normal vascular walls, which were thin and uniform in thickness and brightness (Fig. 1). Interestingly, the LAD wall thickness and external diameter of the vessel were increased to the same extent in patients with angiographically significant LAD stenosis and in patients with subclinical LAD disease. The finding that patients with subclinical LAD disease have equally increased external diameter and wall thickness as patients with clinically significant LAD disease confirms the diffuse nature of coronary atherosclerosis and the presence of arterial remodeling. The presence of arterial remodeling was confirmed by the strong correlation between wall thickness and external diameter of the LAD in patients with CAD (Fig. 4). Detection of outward remodeling gives us another potential way to diagnose subclinical coronary atherosclerosis.

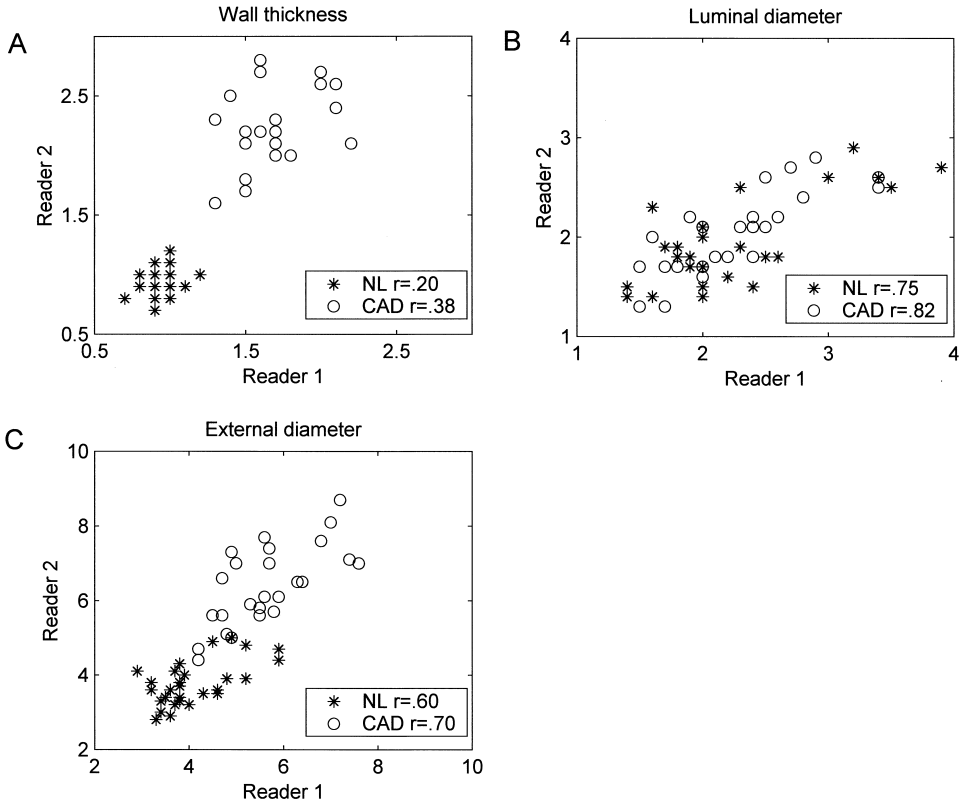

Figure 3. Scatter plot showing the correlation between the two readers as well as relation of wall thickness **(A)** luminal diameter **(B)** and external diameter **(C)** between the groups of normal volunteers and patients with CAD. CAD = coronary artery disease.

Lack of differences in the luminal diameter between the groups is due to the fact that the investigators measured the segments with the largest lumen; thus, in the group of patients with CAD, the most diseased segments with small lumens were not analyzed. Despite that fact, wall thickness and external diameter were found to be different between the group of normal subjects and patients with CAD. An important finding of our study was that, despite measuring

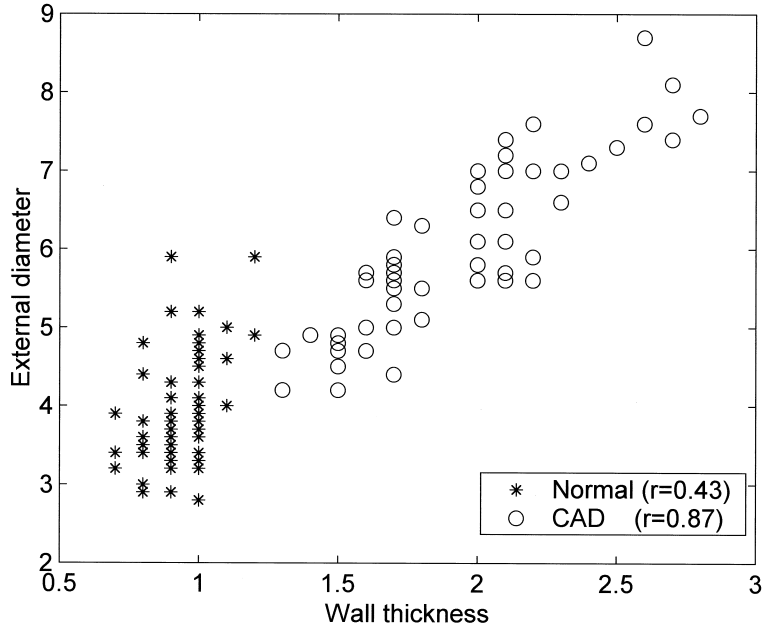

Figure 4. Scatter plot showing the correlation between the left anterior descending coronary artery wall thickness and external diameter in groups of normal volunteers and patients with CAD. CAD = coronary artery disease.

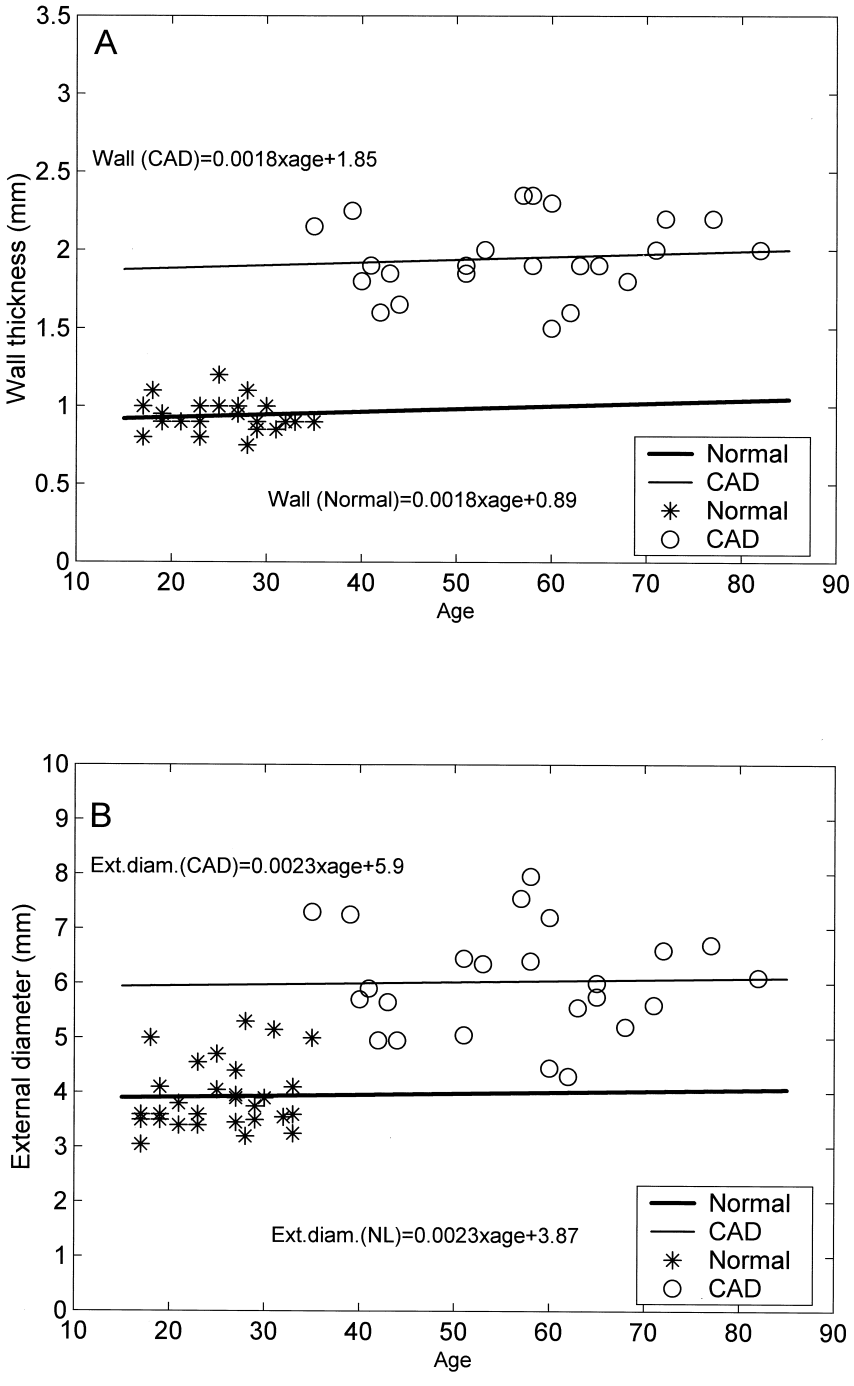

Figure 5. Wall thickness **(A)** and external diameter **(B)** of the left anterior descending coronary artery (LAD) are plotted against age for both normal volunteers and patients with CAD. The effect of age on wall thickness and external diameter of the LAD is very small, as shown by the shallow slopes of the regression lines. CAD = coronary artery disease.

in the location where there was the least amount of plaque by luminal diameter, there was still increased wall thickness in patients with both subclinical and obstructive CAD.

We did not test the sensitivity and specificity of the method in this study since we did not include the entire spectrum of the population, only a group of normal individuals and a group of patients with established diagnosis of CAD. When only the extremes of the population are studied, accurate sensitivity and specificity of the method cannot be estimated.

Comparison with previous work. Our measurements of the LAD wall thickness, luminal size and external diameter are consistent with earlier reports. In one study (14), the wall thickness of the proximal coronary arteries measured by 2DTTE was 1.6 ± 0.3 mm in the group of patients with CAD and 1.2 ± 0.1 mm in normal subjects. Coronary

arterial wall thickness has also been measured using high-frequency epicardial echocardiography (21). In the study by McPherson et al. (21), the wall thickness of normal coronary arteries was 0.56 ± 0.04 mm and that of diseased coronary arteries was 1.6 ± 0.15 mm. In another study (22), intravascular ultrasound (IVUS) was used to measure the external diameter of the LAD in patients undergoing cardiac catheterization. This study demonstrated that vascular remodeling was present in patients who had endothelial dysfunction. The external diameter of the LAD was increased to 5.2 ± 0.3 mm in patients who had an abnormal response to acetylcholine as compared with 3.9 ± 0.3 mm in patients who had a normal response to acetylcholine. Also, an MRI study of coronary arteries (23) reported significant differences in coronary artery wall thickness between normal subjects and patients with CAD. In this study, the average maximum LAD wall thickness in normal subjects was 0.75 ± 0.17 mm and in patients with CAD was 4.38 ± 0.71 mm.

Our measurements of the wall thickness and external diameter are more generous than those reported by IVUS studies and by studies using histological morphometry. However, our results are in concordance with wall thickness reported by previous studies of coronary arteries that used transthoracic echocardiography (14), MRI (23) and epicardial echocardiography (21). The difference in measurements between IVUS and these other techniques comes from the fact that, most likely, HR-2DTTE, MRI and epicardial echocardiographic measurements include all three layers of the coronary artery wall: neointima, media and adventitia, while the IVUS and morphometric measurements excluded adventitia and measured only intimal and medial thickness. It is well recognized that, on IVUS studies, adventitia represents a highly echogenic layer. This highly echogenic layer is most likely also visible on HR-2DTTE, epicardial echocardiography and on MRI.

Study limitations. Intravascular ultrasound studies (24,25) have described the presence of inadequate arterial remodeling or reverse remodeling, which contributes to luminal stenosis in approximately 15% to 20% of patients with CAD. The presence of reverse remodeling may lower the sensitivity of measurements of external diameter of the vessel for detection of CAD; however, it should not affect the sensitivity of wall thickness measurement.

We recognize that we are measuring the thickness of a linear echo, which we assume represents the thickness of the LAD wall. We believe that the linear echo interpreted now as vascular wall represents the full thickness of the vascular wall with neointima, media and adventitia. This hypothesis needs to be verified. We also are not able to state exactly which segment of the LAD is visualized by HR-2DTTE. It, most likely, is a distal part of the proximal LAD and first part of the middle (after first septal perforator) LAD segment, but this possibility also will need to be investigated further. Interrogation of only the LAD represents another limitation. However, CAD is a diffuse process, and the LAD is the most frequently involved vessel, so it should serve as an adequate sample of the coronary vasculature. Based on autopsy and IVUS data (6), the LAD is almost always involved to some extent if CAD is present, and, thus, the LAD should be a very sensitive indicator of CAD.

The imaging technique used in this study provides only longitudinal planes of the LAD. Since coronary atherosclerotic plaque is frequently eccentric, sectioning the vessel with the ultrasound beam in only one plane may miss an eccentric plaque and, thus, lower the sensitivity of the method. Previous studies of lesion morphology using IVUS demonstrated that 69% of all imaged sites had eccentric involvement (26). Ideally one might prefer a cross-sectional view. Unfortunately, in a cross-sectional view, the medial and lateral walls are parallel to the ultrasound beam and, thus, are ultrasonically invisible, which defeats the theoretical advantage of this approach.

Finally, coronary imaging is affected by patient factors known to influence routine echocardiographic image quality. There will be patients in whom the exam is limited by the lack of an available ultrasonic window.

Significance. Obtaining a reliable, noninvasive way to identify subclinical CAD in asymptomatic individuals remains a challenge. However, the clinical and economic implications of instituting preventive therapy in these patients is tremendous and potentially lifesaving. Early knowledge of coronary artery wall changes is vital in achieving progress in managing coronary atherosclerosis.

If verified, this method, which is relatively easy to perform, inexpensive and noninvasive, has the potential to diagnose coronary atherosclerosis at earlier stages and could redefine the indications for aggressive primary prevention.

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